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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,142	05/10/2001	Ilse Bartke	305J-900320US	6801

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EXAMINER	
HANLEY, SUSAN MARIE	
ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 12/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/854,142	BARTKE ET AL.	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,12-15,17,19-23 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-6, 12-15, 17, 19-23 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/7/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants and amendment response filed 10/7/05 is acknowledged. Claims 1, 3-6, 12-15, 17, 19-23 and 25 are presented for examination.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3-6, 12, 13, 17, 19-23 and 25 stand rejected under 33 U.S.C. 103(a) as being unpatentable over Kramer et al. (1995) in view of Urschel et al. (1990), Althaus (WO 9303140), Unger et al. (EP 731,108) and Unger et al. (1995) and in further view of Weiner et al. (US 5,935,577).

Claims 14 and 15 stand rejected under 33 U.S.C. 103(a) as being unpatentable over Kramer et al. (1995) in view of Urschel et al. (1990), Althaus (WO 9303140), Unger et al. (EP 731,108) and Unger et al. (1995) and in further view of Hammang et al. (US 5,904,144) and The Merck Manual (p. 1091). Applicant argued against claim 14 and 15 insofar as the references pertained to the arguments against claims 1, 3-6, 12, 13, 17, 19-23 and 25.

Applicant argues that all of the requirements to establish a case of *prima facie* obviousness have not been met. Applicant asserts that the Office has not established a motivation to combine the references. Applicant asserts that the Office has made an overly broad interpretation of the statement by Unger (EP 731,108) regarding "the identification and characterization ... (col. 1, lines 18-23). Applicant disagrees with the Examiner's conclusion from Unger "that there is a close relationship between regeneration and degeneration" and that "demyelination and remyelination are closely related." Applicant asserts that Unger may imply that increased regeneration of oligodendrocytes would help understand diseases such as MS but the reference does not state or imply that demyelination and remyelination are closely related. Applicant further asserts that MS involves multiple facets and areas, i.e. oligodendrocytes and myelin.

Applicant interprets the Office action at p. 5 as an invitation to experiment to see if something will work but does not establish a case for obviousness.

Applicant further asserts that the cited references do not provide a reasonable expectation of success to achieve the claimed invention because the references employ different specie models for demyelination. Applicant alleges that information derived from a rodent study may not be applicable to humans due to interspecies differences regarding receptors and the biological effects of growth factors. Applicant asserts that the Office's citation of Warner (US 5,935,577) is not valid in view of the statement of the disclosure regarding interspecies differences *supra*. Applicant cites Van Regenmortel (2004) and the National Heart, Lung and Blood Institutes Strategic Plan for YF 2005-9 to support the argument that "animal models of human diseases are not always sufficient to test the efficacy of experimental therapies."

Applicant argues that the references are not being considered individually by stating their differences but instead are demonstrating the different areas of the references and that the combination of the references does not provide an expectation of success. Applicant argues that the combination of the references do not present all of the elements because the Office action does not corroborate the statement that NGF down regulates the production of interferon gamma by T cells.

Responding to Applicant's argument that the Office has too broadly interpreted Unger (EP 731,108), the entire paragraph that comprises the cited quotation discloses at col. 1, lines 10-23 reads:

> The covering of nerve fibers in the central nervous system (CNS) with myelin is essential for the function of neuronal signal transmission. The myelin sheath is formed by oligodendrocytes (OL), the fibers of which wrap around the axon of a nerve cell. Demyelinating diseases such as multiple sclerosis in which the myelin sheath of the axon is damaged or destroyed also lead to impairments of the OL. However, the OL remains capable of regenerating the myelin sheaths. Therefore, the identification and characterization of factors which are responsible for increased regeneration of OL is very important for the molecular understanding of demyelination diseases, such as multiple sclerosis (MS), and for the development of therapeutic agents.

Furthermore, Unger states that it is known from PCT/EP92/01173 that the regeneration of oligodendrocytes is improved when they are treated with NGF or active fragments of NGF.

From this disclosure, it is evident that OL is a significant portion of the myelin sheath and that OL is affected by demyelination and remyelination processes of a nerve. Clearly, the identification of factors that affect remyelination are closely related on "a molecular level" to demyelination diseases. Thus, the conclusion of the Office in the previous Office action is not overly broad. The link by Unger between the two processes is established on "a molecular level." In the case of remyelination, the molecular level is the interaction of NGF with OL. Thus, the skilled artisan would have realized from Unger that the processes of demyelination and remyelination affect the same substrate, OL, and that the characterization of factors for remyelination are likely to have a similar basis with the factors that lead to demyelination. Therefore, Applicant's argument that there is no motivation to combine references due to their various foci is moot because demyelination and remyelination processes are closely related and the ordinary artisan would have expected that results in one area would provide relevant information for a related area of research. This is not an invitation to experimentation. The statement means that the skilled artisan would have naturally viewed information that reported on myelinating processes as relevant to the field of the instant invention.

Addressing Applicant's argument that there is no motivation to combine the references and that the references focus on different areas such that the combination of the references does not provide an expectation of success, Applicant is attacking the references individually and not considering the common elements of the references. Althaus teaches, in the English abstract, that NGF can be used to treat demyelination of nerve fibers as well as improving remyelination of nerve fibers. Thus, Althaus strongly supports Unger (EP 731,108) *supra* in that there is a close relationship between demyelination and remyelination. Kramer et al. disclose that "unexpectedly, exogenous NGF profoundly changes development of the demyelinating inflammatory changes evoked by neuritogenic T lymphocytes during the course of EAN. The reduction of clinical symptoms through the entire course of the disease by using NGF-secreting R4 lymphocytes is faithfully reflected in a corresponding amelioration of lesions in the PNS." (See page 1164, column 2, first full paragraph). Thus, Kramer is directly related to suppressing the

effect of demyelination. Finally, Urschel et al. disclose that suppression of NGF endogenous levels with NGF antibodies results in demyelination. Thus, the ordinary artisan would have recognized that the presence of intact NGF is necessary to maintain myelin and that it would have been obvious to suppress demyelination since the prior makes it clear that NGF is necessary to suppress demyelination as well as for improving remyelination.

Responding to Applicant's assertion that the assertion that NGF would not inherently down regulate the production of interferon-gamma by T cells, Applicant is directed to the disclosure of the Weiner patent (US 5,935,577). Weiner discloses that demyelinating diseases are autoimmune diseases characterized by an abnormal response directed against autologous tissues. Autoimmune diseases such as multiple sclerosis are T-cell mediated (col. 1, lines 10-27). Weiner discloses that the efficacy of treatment of autoimmune diseases is assessed by determining the diminution in certain inflammation markers, including IL-2 or IFN-gamma. A decrease in these markers is indicative of successful treatment (col. 9, lines 25-33). Weiner teaches that T-cells produce IFN-gamma (col. 3, lines 12-13). Thus, the successful treatment of an autoimmune disease will diminish IFN-gamma production. Demyelinating diseases such as MS are T-cell mediated autoimmune diseases. Thus, the suppression of demyelination will inherently suppress the immune response. This is not a new ground of rejection since Weiner was previously cited and the cited disclosure is a reply to Applicant's argument.

Responding to Applicant's argument that the cited references do not provide a reasonable expectation of success to achieve the claimed invention because the references employ different specie models for demyelination, Applicant's argument is unsupported by factual evidence. The statement in the instant specification regarding interspecies differences concerning growth factors and receptor expression and Applicant's references to Van Regenmortel and the Nation Heart, Lung and Blood Institutes do not provide data that specifically rebuts Weiner. Weiner explicitly teaches that the various animal EAE models are regarded as a good approximation of the reaction that a human would have for

taking NGF to suppress demyelination. Applicant fails to provide any specific examples as to why the statement by Weiner et al. is invalid.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

JEAN C. WITZ
PRIMARY EXAMINER

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Susan Hanley
Patent Examiner
AU 1651